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ABSTRACT

This study investigated the cognitive and behavioral functions associated with iron deficiency anemia in infants and toddlers and the short-term effects of therapy on such behaviors. Subjects were 24 iron deficient and anemic infants, 9 to 26 months old. The subjects were randomly assigned to a treatment or control group. The Bayley Scales of Infant Development were administered before the institution of treatment with intramuscular iron or placebo, and the test was readministered in 5 to 8 days. Children treated with iron showed a significant increase, compared to the controls, in their scores on the Mental Development Index. The treated group also became more alert and responsive and demonstrated improvement in tests of gross and fine motor coordination. These findings support the hypothesis that iron deficiency in infants produces developmental alterations and that these changes are rapidly reversible with iron therapy. (Author/SB)

Developmental Scores of Iron Deficient Infants and the Effects of Therapy[1]

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Abstract

A recent HEW report has suggested that iron deficiency anemia may affect 15-20% of children under 18 years. Young children from low income families may be particularly vulnerable to developmental effects such as irritability and attentional and cognitive deficits which have been clinically reported in iron deficient subjects. The present study investigated both the cognitive and behavioral functions associated with iron deficiency anemia in infants and toddlers and the short-term effects of therapy on such behaviors. The subjects were randomly assigned to a treatment and control group. The Bayley Scales of Infant Development were administered before the institution of treatment with intramuscular iron or placebo, and the test was readministered in 5 to 8 days. Children treated with iron showed a significant increase, compared to the controls, in their scores on the Mental Development Index, averaging a mean gain of 13.6 points in a mean time of 6.8 days. The treated group was also found to become more alert and responsive and demonstrated improvement in tests of gross and fine motor coordination. These findings support the hypothesis that iron deficiency in infants produces developmental alterations and that these changes are rapidly reversible with iron therapy.

Developmental Scores of Iron Deficient Infants and the Effects of Therapy

Iron anemia is a condition which may often go undiagnosed in routine pediatric examinations. Yet some reports have suggested that iron deficient subjects have psychological deficits, such as lower IQ scores, decreased attentiveness, restricted perception, and impaired performance on measures of latency and associative reactions (Howell, 1971; Sulzer, Wesley & Leonig, 1973). In a recent study, young adolescents who were iron deficient were found to be more disruptive, irritable and restless in the classroom and to score lower on tests of academic performance than their non-anemic controls (Webb & Oski, 1973, 1974). For some years, physicians have had the clinical impression that irritability is one of the characteristics of the iron deficient subject (Mauer, 1969).

Most studies to date which have attempted to link iron deficiency anemia with negative psychological and behavioral findings have dealt with populations of older children and adolescents. In addition, all iron anemia studies have been criticized as suffering from serious flaws in experimental design (Pollitt & Leibel, 1976).

If the behavioral effects of iron deficiency anemia are prominent and negative, then the importance of directing research efforts to a population of very young children can better be understood. Emotional and cognitive development are closely interrelated in infancy (Bell, 1970; Lally & Honig, 1975; Kohlberg, 1968). Thus, disturbances in emotional behaviors or attention span which have been attributed to iron deficient subjects may quite possibly entail impairment in cognitive developmental functioning as well.

In the present study, we have chosen to study cognitive and emotional behaviors in a sample of infants identified as iron deficient in the course of their attendance at a hospital clinic that serves a low-income population. Such a population may be particularly vulnerable to dietary deficiencies which can lead to iron anemia. The purpose of the study was to identify any developmental deficits associated with iron deficiency anemia and to study the effects of treatment on cognitive and emotional functioning of the infants.

Method

Subjects

Twenty-four infants (ranging in age from 9 to 26 months) were selected for study from the Pediatric Ambulatory Department at the State University Hospital of the Upstate Medical Center in New York

State. Occupational status of the parents was quite similar for all infants. Most of the parents were unemployed. The others held unskilled or semiskilled jobs such as factory packer or waitress. The mean number of years of education for the parents was 10.6.

All subjects were iron deficient and anemic as judged by the following criteria: hemoglobin of less than 10.5 gm/dl; MCV[1] of 73 μ^3 or less; serum iron concentration of 50 μgram/dl or less; and serum transferrin saturation[2] of 12% or less. All subjects were free of intercurrent illness at the time of study, and none had a recognizable chronic illness. All had blood lead concentrations of less than 30 μgm/dl. Dietary histories of the infants in this study indicated that all infants were bottle fed and none had been breast fed.

After obtaining informed parental consent, the iron deficient infants were randomly assigned either to the control group or to the experimental group in accordance with Campbell and Stanley's (1966) Pretest-Posttest Control Group Design 4.

As can be seen in Table 1, the control and experimental

Insert Table 1 about here

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groups did not differ with respect to sexual or racial composition or mean education level attained by parents. The range of maternal education differed somewhat due entirely to one control mother who had had no formal schooling. The control and experimental groups were similar with respect to age, weight, initial hemoglobin concentration, red cell MCV, serum iron and percent transferrin saturation. Mean number of days elapsing between test and retest differed somewhat between the two groups due entirely to one control subject whose parent was repeatedly unable to keep appointments so that the retest interval for that child was 30 days.

Procedures

Hematologic determinations for each infant were performed on a Coulter Counter, Model S. Serum iron and total iron binding capacity were performed by the method of Jung and Parekh (1970).

All subjects had two psychological examinations with the Bayley Scales of Infant Development (Psychological Corporation, 1969). Both the Mental Scale and Motor Scale were administered and the Infant Behavior Record completed at each pre and posttesting session. During every examination, at least one parent was present. Every effort was made to maintain optimal testing conditions. When necessary, this meant bottle feeding the infant or spending sufficient time to help the infant feel fully at ease in the testing situation prior to examination. Neither the examiner (ASH) nor the nurse who later administered injections was informed as to which group any infant belonged until the test-retest battery was completed and the Bayley protocols had been scored.

Following the initial psychological testing, in order to control for any unknown effects of an injection procedure, the control group received a placebo of sterile saline intramuscularly while the experimental group received an intramuscular injection of an iron-dextran complex, Imferon. The dose of intramuscular iron was calculated to provide sufficient iron to raise the hemoglobin level to 12 gm/dl and provide extra iron to replenish body iron stores. Appointments were made for parents to bring their children back for a second visit within 5 to 8 days of the initial testing visit. During the return visit, immediately after the psychological examination, subjects who had initially received the placebo were also treated with intramuscular iron.

Results

Developmental Scores

Initial Bayley scores for the Mental Development Index (MDI) and the Physical Development Index (PDI) were similar in the two groups (Table 2). Following iron therapy, the experimental group

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Insert Table 2 about here

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demonstrated a significant mean gain of 14 points ($p = .01$) on their MDI. A t test of the control group's gain of 6 MDI points on retest was not significant. A t test of the mean difference in test-retest scores between experimental and control infants on the Mental Development Index was significant at $p < .05$ level. For the Physical Development Index (PDI) there was a mean gain of 11.4 points for experimental infants. A t test indicated that this difference did not reach statistical significance ($p = .10$) and neither did the control group's mean retest gain of 3.7 PDI points.

In the experimental group, 8 of the 12 subjects gained an increase of 10 or more MDI points on the retest, while only 3 of the 12 control subjects registered such an increase ($p = .05$).

Thus, on the infant developmental tests, the experimental group clearly improved in cognitive scores, in comparison to their non-treated controls, within one week of receiving iron treatment.

In order to check further into the relationship between iron anemia deficiency and the changes observed in cognitive function, a Pearson correlation coefficient was computed between the magnitude of the MDI change scores from pre to posttest and the magnitude of the initial hemoglobin level. No relationship between change in score and initial hemoglobin level was found for control infants. In contrast, there was a strong inverse correlation in the iron treated group between magnitude of increase in MDI scores and initial hemoglobin level (r= -0.72, p= .01). Since the initial status of severity of iron deficiency was unknown to the tester, this correlation again tends to confirm that iron therapy may be responsible for positive changes in developmental test scores, particularly for those infants who are initially most severely at risk for iron deficiency anemia.

Behavioral Scores

Specific items on the Bayley Infant Behavior Record were analyzed to provide information about noncognitive behavioral areas where decrement in functioning has been clinically suspected.

Since irritability has been identified clinically as a possible concomitant of iron deficiency, an analysis of Bayley Item 15 (Reactivity) is of particular interest. Infants are rated as underreactive (scores 1, 2, 3, 4), normally alert and responsive to the test situation and materials (scores 5, 6, 7), or overreactive and overly sensitive to stimuli in the test situation (scores 8, 9). The majority of the iron deficient infants in both groups did not achieve pretest scores of 5, 6, or 7, which represent the normal range and the modal score nationally for infants in the age group of our sample. Table 3 shows that there were positive

Insert Table 3 about here

changes from pre to posttest among the experimental infants such that ratings of 4 of the 12 experimental infants changed from abnormally reactive on the pretest to normal alertness and responsiveness at posttest. Only one of the 12 control infants received either a pretest or a posttest rating in this normal range. On the posttest, very low reactivity to test stimuli and, in one case, overexcitability characterized the responses of 11 of the 12 control infants. Only four of the experimental infants were scored as rather insensitive to the usual test stimuli, and none was scored as over-reactive on the posttest. The Fisher's exact test probability for these differences is $p = .018$.

Bayley Item 12 (Attention Span) was also analyzed since this behavioral characteristic has been cited as affected by iron deficiency anemia. Bayley norms indicate that nationally more than 80% of infants in the age range of our sample attain an adequate or superior rating of attention span (a score of 5 or higher on the nine point scale). On the pretest, 10 of the 12 controls and 6 of the 12 experimentals scored below the modal national score of 5. Thus, these data are somewhat supportive of the hypothesis that iron deficiency is associated with impaired attention span. However, on posttest, 8 controls and 5 experimentals still scored below the national mode. Thus, our results do not support the hypothesis that iron therapy leads promptly to behavioral changes toward increased adequacy of attention span in infants.

Interesting changes in the motoric competence of the infants who received iron therapy were suggested by the data. These changes were reflected in the scores for Bayley Scale 26 (Coordination of Gross Muscle Movements) and Scale 27 (Coordination of Fine Muscles). Half of the infants in each group received a poor gross motor rating on the pretest (that is, scores of 4 or 5 on a 5 point scale where 5 was the poorest and 1 was the best coordination score). On the posttest, this ratio remained the same for the control group, but only two of the 12 experimentals still performed at the poorest levels with respect to gross motor coordination ($\chi^2 = 6.64$, $p = .01$).

Changes in the fine motor coordination ratings as a function of iron therapy were equally intersting. Seven controls and six experimental infants on the pretest attained the poorest score, 5 (on a 5 point scale where 1 is the best score). On the posttest, only 1 experimental infant, in contrast to 5 controls, still received the poorest score ($\chi^2 = 5.44$, $p = .02$). Thus, our data do suggest a tendency for iron anemia to be associated with coordination deficits. Clinically, for example, this could be seen in the case of one infant, who persisted but was not able to place one block atop another in the pretest but within a week after iron therapy was able to build a three-block tower.

Discussion

This study demontrated that treatment of iron deficiency in young children produces a quantifiable improvement in measures of psychological performance within one week. Improvement was particularly found on the Mental Development Index of the Bayley Scales of Infant Development.

There was also an increase in the number of experimental infants characterized as normally reactive and alert to the test stimuli and situation on the posttest. The pretest scores of a majority of the iron deficient infants were predominantly under-reactive. This lack of reactivity to test stimuli could be interpreted as contradictory to the "irritable reactivity" mentioned so prominently as a clinical indicator of iron anemia deficiency. However, clinical irritability does not preclude a relative "tuning out" by infants of the tasks and presentations of the testing situation. Indeed, during the examinations, a lot more effort was often required by the tester to induce iron deficient infants to respond to the test toys which are generally highly attractive to infants. The iron deficient child has been clinically characterized not only as "irritable" but also as "listless" and typically showing "a lack of interest in surroundings" (Mauer, 1969, p. 205). Thus the present findings are consistent with clinical medical judgments.

Whether the findings of significant improvement following iron therapy, in overall gross and fine motor coordinations, are more than a chance occurrence among 29 Bayley Behavior Record items scored, will need to be evaluated in further studies of iron-deficient infants.

The seriousness of the problem of iron deficiency as it relates to child development must be considered in the light of recent assertions by the United States Department of Health, Education and Welfare (1972) that approximately 15-20% of children in the United States under the age of 18 years are iron deficient. The incidence of iron deficiency is highest among lower socioeconomic groups. Infants one to three years of age are particularly vulnerable since caregivers may not be aware of the nutritional needs of infants for iron in the diet. Also, high irritability plus lack of responsiveness to proferred toys and games on the part of the iron anemic infant may adversely affect the quality of adult caregiving and social interactions the infant subsequently receives. This distortion in the caregiving pattern can place an infant even further developmentally at risk. Some support for long range effects of deficit have been reported. Cantwell (1974) found that children who were iron deficient between 6 and 13 months of age were found at 6 to 7 years of age to be more clumsy, less attentive, and more hyperactive than a similar group of children who were not iron deficient during the first 2 years of life.

Our study suggests that deficits in cognition and emotional reactivity may be rapidly reversible if treated during the first two years of life. Further research on greater numbers of infants is needed to confirm this finding. Certainly it also remains to be demonstrated if deficits are always correctible after long-term iron deficiency. Certainly it would be entirely unethical to deprive a control group of iron therapy for a lengthy time period. Thus it is difficult to speculate on the question of whether rapidly reversible effects are sustained among experimental infants in comparison to controls. Whether the effects of iron therapy are sustained over a lengthy time period among treated subjects is also of interest. Follow-up data of this nature were, however, not available for these children. In any case, the implications of this study should alert care-giving personnel to the importance of early check-ups for iron deficiency anemia among infants, particularly where developmental growth patterns do not appear optimal.

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Footnotes

[1]MCV, or Mean Cell Volume, is a measure of the size of the red cells. Patients with iron deficiency anemia have small red cells.

[2]Transferrin is the protein in the blood that transports iron. A low serum transferrin saturation indicates the presence of iron deficiency.

Table 1

Initial Characteristics of the

Control and Experimental Groups[a]

Characteristic	Control (N = 12)	Experimental (N = 12)
Sex		
Male	8	8
Female	4	4
Race		
Black	6	6
White	6	6
Mother's Education (years)	10	10.5
	(0 - 14)	(7 - 13)
Father's Education (years)	11	11.1
	(10 - 13)	(9 - 14)
Weight (kg)	11.30 ± 1.32	11.94 ± 1.37
	(8.6 - 12.4)	(7.9 - 12.8)
Age (months)	14.37 ± 3.45	16.29 ± 3.57
	(9 - 19)	(12.5 - 26)
Hemoglobin (gm/dl)	8.95 ± 0.86	8.73 ± 1.09
	(7.6 - 10.1)	(6.2 - 10.3)
Serum iron (μgm/dl)	25.3 ± 12.0	25.8 ± 11.3
	(6 - 39)	(13 - 51)

(Table 1 cont'd.)

Characteristic	Control (N = 12)	Experimental (N = 12)
Transferrin saturation (%)	5.41 ± 2.7	4.95 ± 2.0
	(1 - 11)	(2 - 8)
MCV (μ^3)	60.0 ± 6.5	56.6 ± 5.5
	(54 - 73)	(49 - 67)
Days to retest	9.75 ± 6.6	6.83 ± 1.5
	(6 - 30)	(5 - 10)

[a] Values represent mean plus or minus one standard deviation. Values in parentheses represent range of values.

Table 2

Bayley Test Scores[a]

Group and Test	Pretest	Posttest
Control		
Mental Development Index	90.58 ± 15.00	96.66 ± 17.36
	(64 - 112)	(68 - 126)
Physical Development Index	93.08 ± 16.15	97.25 ± 17.21
	(61 - 110)	(65 - 119)
Experimental		
Mental Development Index	96.25** ± 9.82	109.83** ± 9.18
	(83 - 116)	(97 - 122)
Physical Development Index	96.41* ± 12.68	107.41* ± 14.06
	(76 - 118)	(85 - 125)

[a]Values represent mean plus or minus one standard deviation. Values in parentheses represent range of all values.

*p = .10

**p = .01

TABLE 3

Changes from Pre to Posttest in Reactivity Scores on the Bayley Infant Behavior Record

Bayley Rating	Control Group Pre	Control Group Post	Experimental Group Pre	Experimental Group Post
1, 2, 3, 4 (Unreactive ; responds only to strong and repeated stimulation with test materials and presentations.)	11	10	7	4
5, 6, 7 (Moderate to quite alert and responsive.)	1	1	4	8
8, 9 (Overexcitable; startles quickly; overly sensitive to stimuli.)	0	1	1	0